## REMARKS/ARGUMENTS

Status of the Claims

Claims 1, 6, 7, 10, 11, 44, 49-51 and 108-114 were pending. Claims 1-43, 45-49, 52-110 and 112 are canceled without prejudice or disclaimer. Applicants reserve the right to prosecute the canceled subject matter in a divisional or continuation application. Claims 44, 50 and 51 are withdrawn as drawn to a non-elected invention. New claim 115 is added herein. Claims 111 and 113-115 are presently under examination.

Claim Amendments

Claims 44 and 50 are amended to avoid dependence from canceled claims.

Claim 111 is amended to incorporate the limitations of previously dependent claim 112. Claim 111 is further amended to delete the phrase, "wherein administration of the naked hMN-14 antibody to a cancer expressing CEA sensitizes the cancer to administration of an apoptosis agent" to reduce issues for consideration on appeal.

Claim 114 is amended to recite that the apoptosis agent is selected from the group consisting of DTIC and CPT-11. The amendment is supported in the Specification at least in Examples 2, 6, 7-9 and 14-17. Claim 114 is also amended to recite that the anti-CEA MAb is a Class III anti-CEA MAb that binds to CD66(e). The amendment is supported in the Specification at least at Paragraphs [0002], [0008] and [0046]. Claim 114 is further amended to recite an IgG1 antibody. The amendment is supported in the Specification at least at Paragraphs [0066], [0074] and [0284].

New claim 115 is added to recite the composition of claim 111, wherein the apoptotic agent is 5-fluorouracil/leucovorin. The amendment is supported at least by original claim 95 and in the Specification at least at Paragraphs [0101], [0103]-[0105], [0107] and [0211].

Applicants submit that no new matter is added by amendment.

### Claim Rejections – 35 U.S.C. 112 1st Paragraph

Claims 1, 6, 7, 10, 11, 108-112 and 114 were rejected under 35 U.S.C. 112, 1st paragraph. The Action asserts that the application is, "lacking enablement for any combination therapy (any anti-CEA antibody with any apoptotic agent) producing a synergistic effect in treating human medullary thyroid carcinoma or human colorectal carcinoma." The Action further asserts that, "the specification does not reasonably provide enablement for using any anti-CEA antibody to sensitize any cancer in vivo to a therapeutic agent much less where the subject is a human."

Applicants note that each of the claims presently under consideration is limited to either a naked humanized MN-14 MAb comprising the 6 MN-14 CDR sequences (claims 111 and 113) or a naked humanized, chimeric or human MAb that binds to the same epitope of CEA as the MN-14 antibody. The epitope of CEA to which MN-14 binds is identified as CD66(e) (and not CD66(a-d)). Further, amended claim 111 no longer requires that the antibody sensitize the cancer to the apoptotic agent, but merely refers to a synergistic effect between the hMN-14 antibody and a short list of apoptotic agents, including DTIC, CPT-11 and 5-fluorouracil/leucovorin.

The claims under examination no longer recite any apoptotic agent, but rather are limited to either DTIC or CPT-11 (claims 113 and 114); the group consisting of vincristine, doxorubicin, dacarbazine (DTIC), cyclophosphamide, CPT-11, oxaliplatin, 5-fluorouracil/leucovorin and gemcitabine (claim 111); or 5-FU/leucovorin (claim 115).

The synergistic effect of DTIC and CPT-11 with hMN-14 in treating human medullary thyroid carcinoma or human colorectal carcinoma is well documented in the instant Application, as is the effect of hMN-14 in sensitizing CEA-expressing cancers to DTIC and CPT-11. As noted in the last response to Office Action, Example 2 states that in treating human medullary thyroid tumor cells, "Surprisingly, the effects of MN-14 alone and DTIC alone were not additive...given the results of treatment with 250 μg hMN-14 and 100 μg DTIC alone, one would not predict that the combination of 250 μg hMN-14 and 100 μg DTIC would have such a pronounced effect." Further, "The 75 μg dose of DTIC in combination with this schedule of hMN-14 antibody was significantly more effective than either treatment alone." In conclusion, "Combined therapy of the naked anti-CEA antibody with DTIC augments the anti-tumor effects of antibody or chemotherapy alone, without increased toxicity."

Example 7 reiterates that for treatment of medullary thyroid carcinoma, "The 75 μg dose of DTIC in combination with this schedule of hMN-14 was significantly more effective than either treatment alone ($P<0.02$)...combined therapy of the naked anti-CEA MAb with DTIC augments the anti-tumor effects of antibody or chemotherapy alone, without increased toxicity." Example 8 states that, "When combined with DTIC, a surprisingly enhanced level of inhibition of tumor growth occurred relative to either treatment alone."

Example 9 discusses the *in vivo* effects of antibody-induced chemosensitization of cancer cells and concludes, "The results show that co-administration of hMN-14 and CPT-11 to nude mice bearing GW-39 lung micrometastases [of colon cancer cells] increases survival beyond the effect of either modality alone." Further, "the results demonstrate that the 3-day pretreatment with hMN-14 followed by CPT-11 increased median survival to 105 days ($p<0.001$), compared with CPT-11 alone on day 3, with a median survival of 70 days."

Example 14 discloses that for an advanced colon cancer model, "No effect of hMN-14 by itself is apparent under these conditions, and only a modest effect of CPT-11 ($p<0.05$) was observed...Combination therapy with hMN-14 CEA MAb and CPT-11 significantly prolongs survival of an animal with advanced human colonic tumor metastasis." Examples 15-17 confirm the synergistic effects of hMN-14 and CPT-11.

Applicants further submit that 5-FU has been demonstrated to show a synergistic effect with anti-CEA antibody, as evidenced by Blumenthal et al. (2005, Cancer Immunol Immunother 54:315-27, Abstract attached). As stated in the Abstract of Blumenthal, "When nude mice received labetuzumab (hMN-14) with CPT-11 or 5FU, median survival increased significantly as compared to the drug or antibody alone," and "The MAb also shows chemosensitizing properties." Although the Blumenthal publication is dated after the instant filing date, it is submitted not to provide enablement support for the pending claims, but rather to demonstrate that the claimed invention works for its intended purpose, as recited in claims 111 and 113-115. Applicants submit that therapy of cancer patients with 5-FU was extremely well known in the art as of the instant filing date and therapy with compositions comprising anti-CEA MAbs and apoptotic agents was enabled by the instant application. The only question is whether or not the apoptotic agents listed in claim 111 in fact exhibit synergistic effects with hMN-14. The Blumenthal publication demonstrates that such a synergistic effect in fact occurs. Under MPEP 2164.05, the evidence as a whole must be considered in determining enablement, including after filing evidence.

> To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments

> used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention.

Claims 113 and 114 are limited to the apoptotic agents DTIC and CPT-11, for which ample evidence is provided in the filed application concerning synergistic effects. Claim 115 is limited to 5-FU/leucovorin, for which the Blumenthal publication demonstrates that a synergistic effect as recited and enabled by the instant application actually exists. Applicants respectfully submit that the species of DTIC, CPT-11 and 5-fluorouracil are a representative number of species of the Markush group genus recited in claim 111, which only contains a total of eight species.

The enablement of synergistic effects and/or sensitizing effects of hMN-14 has been amply demonstrated in the Examples cited above. Claim 114 is amended to recite IgG1, Class III anti-CEA antibodies that bind to the same epitope of CEA as the MN-14 antibody. The Specification provides ample description and support for antibodies binding to that epitope of CEA, stating in Paragraph [0002] that, "In particular, the invention relates to methods of treating cancers that express CEA by administering, prior to, with or after administering the therapeutic agent, a Class III anti-carcinoembryonic antigen ("anti-CEA") monoclonal antibody ("MAb"), particularly a MAb, that has the binding affinity characteristics and specificities of corresponding murine Class III anti-CEA MAb."

The Specification explicitly defines Class III MAbs and distinguishes them from Class I and Class II anti-CEA MAbs in Paragraph [0008], "Another embodiment includes Class II anti-CEA Mabs or fragments thereof, that may react with CD66a, b and d but not CD66c or Class I Mabs or fragments thereof, that react with CD66a, b, or d as well as CD66c (by definition a Class I Mab binds with CD66c)." Also at Paragraph [0047], "Class II Mabs that are not CD66a-d cross-reactive. These are Mabs that are reactive with CEA domains N-A1B1, A2B2, which do react with Meconium Antigen, but not with NCA, and do not react with granulocytes. For example, NP-3 and MN-6 are Class II anti-CEA antibodies useful in the present invention. Additionally contemplated for use in the present invention are Class II anti-CEA Mabs or fragments thereof, that may react with CD66a, b and d but not CD66c or Class I Mabs or fragments thereof, that react with CD66a, b, or d as well as CD66c (by definition a Class I Mab binds with CD66c)."

A definition of Class III MAbs is found in Paragraph [0046], which states that, "As used herein, the phrase 'Class III anti-CEA' antibody or antibody fragment means an antibody or fragment that binds the CEA antigen (or CD66e) and is unreactive with normal cross-reactive antigen (NCA), meconium antigen (MA), granulocytes and CD66a-d (see, Primus et al., U.S. Pat. No. 4,818,709, incorporated by reference)."

Thus, a Class III anti-CEA antibody is one that binds to CD66(e) but not to CD66(a-d) and is unreactive with the NCA and MA antigens. An IgG1 chimeric, humanized or human antibody, as well known in the art, is one that contains constant region sequences from a human IgG1 antibody. An example of an IgG1, Class III antibody is hMN-14, as disclosed in the Specification at Paragraphs [0009], [0066] and [0284].

As stated in the "Revised Interim Written Description Guidelines Training Materials" in Example 16, "The level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was conventional. This is a mature technology where the level of skill is high and advanced." Thus, the Office recognized that production of additional antibodies against a well-characterized epitope of a target antigen, such as CD66(e) of the carcinoembryonic antigen, was a matter of routine experimentation in the art.

Applicants respectfully submit that IgG1 antibodies binding to the CD66(e) epitope of CEA would be reasonably expected to exhibit the same pharmacologic characteristics as the MN-14 antibody, which also binds to the CD66(e) epitope of CEA and is an IgG1 antibody, and that it would be well within the level of routine experimentation for a person of ordinary skill in the art to make such antibodies and to determine whether or not a particular anti-CEA MAb binds to the same epitope of CEA as MN-14. Since claim 114 is limited to the apoptotic agents CPT-11 and DTIC, Applicants submit that the scope of claim 114 is fully enabled by the instant application.

Applicants note that claim 113 was considered by the Action to satisfy the requirements of 35 U.S.C. 112, 1st paragraph. Applicants respectfully submit that considering the greatly reduced scope of the amended claims, the level of enablement provided in the instant Application is fully commensurate with the scope of the claims. Reconsideration and withdrawal of the rejection are respectfully requested.

## Conclusion

For the reasons stated above, Applicants submit that the amended claims are in condition for allowance and request withdrawal of the rejections.

Respectfully submitted,

/Richard A. Nakashima/

Dated: February 23, 2009

Richard A. Nakashima
Reg. No. 42,023
Phone: 303-828-4924